REMARKS

Claims 1-5, 7-13, and 20-28 are currently pending in the present application. Claims 6, 14-19, and 24 were previously cancelled without prejudice. New dependant claims 25 to 28 have been added. These new claims recite the same limitation as claim 9, but depend from independent claims 20 to 23, respectively. No new material has been added.

The present action is the third time that new grounds for rejection have been raised by the Office. Applicants have overcome all grounds for rejection raised in the two previous Office Actions. However, the Office has again raised new grounds for rejecting the claims, this time under § 103(a). For the reasons described below Applicants submit that the rejections in the current action should also be withdrawn.

The claims are directed to a method for delivering to a target cell an oligonucleotide that is 12 to 24 nucleotides in length by first introducing the oligonucleotide or a plasmid expressing an oligonucleotide in to a donor cell in vitro and second contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel comprising connexin 43 with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell by traversing the gap junction. Unlike the art cited in the current Office Action, the claimed method is not directed to introducing an oligonucleotide or plasmid expressing an oligonucleotide into a donor cell for the purpose of studying the effects of the oligonucleotide on the donor cell.

Attached hereto is a Declaration by Dr. Ira Cohen that address the state of knowledge of a person of ordinary skill in the art at the time of filing regarding size limitations on a molecules ability to permeate gap junctions. Dr. Cohen's declaration also confirms that the antisense RNAs described in Rosenthal et al. (Biochimie, 1995 Vol. 77:439-443) and Giampuzzi et al. (Journal of Biological Chemistry, 2001 Vol. 276, pp. 29226-29232) will not traverse a gap junction, as recited by the present claims.

I. First Rejection Under 35 U.S.C. § 103(a)

In the Office Action dated October 28, 2009, the Examiner alleges that claims 1-5, 7-9, 11, 12, and 20-23 are unpatentable under 35 U.S.C. 103(a) over Rosenthal et al. (Biochimie, 1995 Vol. 77:439-443), as evidenced by Salomon et al. (Journal of

Investigational Dermatology, 1994 Vol. 103(2), Abstract only), in view of Hammond et al. (Nature Reviews. Genetics, 2001 Vol. 2:110-119).

The Office Action acknowledges that "Rosenthal et al. do not explicitly state that the oligonucleotide is delivered to the target cell from the donor cell by traversing the gap junction" (Office Action dated Oct. 28, 2009 at p. 5). Rather, the Office takes the position that Rosenthal et al. implicitly teach the claimed method stating that the Office is "interpreting that the oligonucleotide is delivered to the target cell from the donor cell by traversing the gap junction, absent evidence to the contrary" (Office Action dated Oct. 28, 2009 at p. 5). The Office further states that "it falls to Applicant to determine and provide evidence that the oligonucleotide taught by Rosenthal et al. is or is not delivered into the target cell from the donor cell by traversing the gap junction as instantly claimed." (Office Action dated Oct. 28, 2009 at p. 6).

A. The Office Has Failed to Establish a Prima Facie Case

The Office states that "Applicant is reminded that the burden of establishing whether the teachings disclosed by Rosenthal et al. would have the additional function of delivering the oligonucleotide into the target cell from the donor cell by traversing the gap junction under generally any assay conditions falls to Applicant. See MPEP 2112.01." However, before the Office can shift the burden to the applicant, it must present a prima facie case. For the reasons described below, Applicants submit that the Office has failed to present a prima facie case.

The assertions by the Office are not sufficient to establish a prima facie case of obviousness. The Office states that "since the method steps recited in Applicant's claims are the same method steps as taught by Rosenthal et al., the Examiner is interpreting that the oligonucleotide is delivered to the target cell from the donor cell by traversing the gap junction, absent evidence to the contrary." However, the Office must provide a rationale or evidence tending to show inherency. The fact that a certain result may occur in the prior art is not sufficient to establish the inherency of that result (*See* MPEP 2112; *See also Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990), which states "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art" (emphasis in original).

In the present Office Action, no such basis has been provided and therefore no prima facie case has been established. In this regard, Applicants note that the claims were previously amended to recite oligonucleotides that are 12 to 14 nucleotides in length in contrast to the PADPRP antisense RNA used by Rosenthal et al., which is over 3,900 nucleotides in length. As discussed below and explained in the attached Declaration by Dr. Ira Cohen, the antisense oligonucleotides in Rosenthal et al. would not traverse a gap junction. Further, the evidence of record, as discussed below, indicates that one of skill in the art would not even have expected that oligonucleotides 12 to 24 nucleotides in length (including siRNAs) would traverse gap junctions.

B. None of the References Cited Teach or Suggest the Claimed Methods

None of the references cited teach or suggest a method of delivering an oligonucleotide into a target cell comprising: a) introducing the oligonucleotide or a plasmid expressing the oligonucleotide into a donor cell in vitro; and b) contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel comprising connexin 43 with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell by traversing the gap junction and wherein the oligonucleotide is 12-24 nucleotides in length. The cited art does not teach or suggest the claimed methods for at least the reasons described below.

1. Rosenthal et al. Do Not Teach or Suggest the Claimed Methods

The methods recited by Rosenthal et al. are designed to study the effect of blocking the expression of a target gene only in the cells expressing the antisense oligonucleotide and not in any other cells (*i.e.*, not in the dermis of the nude mouse). Rosenthal et al. study the effects of selectively lowering the levels of PADPRP enzyme in cultured human keratinocytes by stably expressing the PADPRP antisense RNA (including the entire PADPRP untranslated and translated regions in antisense orientation) in the cultured human keratinocytes (*see* Rosenthal et al. at p. 440 and Fig. 1). Keratinocytes expressing PADPRP antisense RNA were used to form a reconstituted epidermis grafted on nude mice in order to study the role of the PADPRP in the reconstituted grafted epidermis. Rosenthal et al. do not teach or suggest a method of delivering an oligonucleotide into a target cell comprising: a) introducing the oligonucleotide or a plasmid expressing the oligonucleotide into a donor cell in vitro; and b) contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap

junction channel composed of connexin 43 with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell by traversing the gap junction and wherein the oligonucleotide is 12-24 nucleotides in length. In fact, the stated purpose of the experiments in Rosenthal et al. was to develop a system to examine the role of PADPRP in differentiation and DNA repair by lowering expression of PADPRP in cultured human keratinocytes and in reconstituted human epidermis. Further, the methods described by Rosenthal et al. were not designed or intended to study the effects of PADPRP antisense in the nude mouse dermal layers adjacent to the reconstituted skin grafts. Therefore, the Office's assertion that Rosenthal et al. implicitly practice the claimed methods is contrary to the teachings of Rosenthal et al. For this reason, Rosenthal et al. do not teach or suggest the methods of the present invention.

2. The Office Has Not Shown That the "Donor Cells" in Rosenthal et al. Form Gap Junctions Composed of Connexin 43 with "Target Cells."

The Office Action states that "the human epidermal keratinocyte cells expressing the cDNA antisense oligonucleotide construct are the donor cells as recited in Applicant's claims" (Office Action dated Oct. 28, 2009 at p. 5). Further, the Office Action states that "epidermal keratinocyte cells express endogenous levels of connexin 43 as evidenced by Solomon et al." (Id.). Regarding target cells, the Office states "the nude mice represent target cells that come into contact with the aforementioned donor cells" (Id.).

In fact, from the articles cited by the Office there is no reason to believe that the reconstituted epidermis described in Rosenthal et al. forms gap junctions composed of connexin 43 with the underlying dermis of the nude mouse receiving the graft. The Office cited the Abstract of Salomon et al. to support that keratinocytes express connexin 43. However, the Solomon et al. Abstract discloses that the amount of connexin 43 expressed by keratinocytes depends upon the layer of the epidermis with keratinocytes in some layers expressing no connexin 43. Further, the Solomon et al. Abstract states that connexin 43 "expression was minimal in the basal layer," which is the lowest layer of the epidermis and thus the layer adjacent to the nude mouse dermis. Therefore, if anything, Solomon et al. provides evidence that gap junctions composed of connexin 43 will not form between the basal layer of the reconstituted epidermis and the dermal layer of the nude mouse. For this reason also, Rosenthal et al. do not teach or suggest the methods of the present invention.

3. The Antisense RNA Used by Rosenthal et al. Will Not Traverse Gap Junctions

The Office takes the position that Rosenthal et al. implicitly teach the claimed method stating that the Office is "interpreting that the oligonucleotide is delivered to the target cell from the donor cell by traversing the gap junction, absent evidence to the contrary" (Office Action dated Oct. 28, 2009 at p. 5). The Office further states that "it falls to Applicant to determine and provide evidence that the oligonucleotide taught by Rosenthal et al. is or is not delivered into the target cell from the donor cell by traversing the gap junction as instantly claimed." (Office Action dated Oct. 28, 2009 at p. 6).

However, the antisense RNA disclosed by Rosenthal et al. contains the entire PADPRP untranslated and translated regions in antisense orientation. Thus, this PADPRP antisense RNA is about 3,900 nucleotides in length. As explained in the Rule 1.132 Declaration by Dr. Ira Cohen, attached hereto, an antisense RNA of that length will not traverse a gap junction. Thus, even if the reconstituted epidermis expressing the PADPRP antisense RNA could form gap junctions with the nude mouse dermis, the antisense RNA could not cross the gap junctions (see the Declaration of Dr. Cohen at ¶¶ 10-12). For this reason also, Rosenthal et al. do not teach or suggest the methods of the present invention.

Moreover, in a previous rejection based on 35 U.S.C. § 112 ¶ 1, which was withdrawn in the present Office Action, the Office characterizes Valiunas et al. as teaching limitations on the length of oligonucleotides that can traverse a gap junction.[1] For example, the previous Office Action states:

> The Examiner has found in the prior art that **only oligonucleotides of 12-24 nucleotides in lengths are able to traverse gap junctions composed of Cx43**. See Valiunas et al. (J. Physiol 568.2:459-468, 2005).

Office Action dated July 6, 2009 at 8 (emphasis added).

> Thus, although the specification contemplates the use of any oligonucleotide, including plasmid DNA expressing oligonucleotides, such a disclosure would not be considered enabling since **Valiunas et al. teach that the length of the**

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[1] While not conceding the Examiner's characterization of Valiunas et al., the present claims were amended without prejudice to recite oligonucleotides of 12 to 24 nucleotides in length. As indicated below, the data presented by Dr. Cohen in the attached Rule 1.132 Declaration, demonstrates that the PADPRP antisense oligonucleotide of Rosenthal et al. would not traverse a gap junction.

> **oligonucleotide plays an important factor in gap junction traversal.**

Id. at 9 (emphasis added).

> As the reference of Valiunas et al. above indicates, **the rate of gap junction channel traversal is dependent on the length of the oligonucleotide**.

Id. at 10 (emphasis added). Thus, according to the previous action Valiunas et al. provide evidence that only oligonucleotides 12 to 24 nucleotides in length can traverse a gap junction. However, in the current Office Action the Office is asserting that absent evidence to the contrary, an antisense oligonucleotide that is about 3,900 nucleotides in length is able to traverse a gap junction. For the reasons provided, the Office has not established a prima facie case and in any event, the antisense RNA disclosed by Rosenthal et al. will not traverse a gap junction were one present.

C. One of Skill in the Art Would Not Have Been Motivated to Substitute an siRNA for the Antisense RNA Used by Rosenthal et al.

The Office Action states that "Hammond et al. teach that antisense and RNA interference are two methods of silencing expression of a gene and that RNA interference possesses characteristics that make it superior to antisense" (Office Action dated Oct. 28, 2009 at p. 6).

However, one of skill in the art would not have been motivated by the teachings of Hammond et al. to substitute a siRNA for the antisense RNA used by Rosenthal et al. to reduce expression of PADPRP In fact, according to Hammond et al. RNAi was "a tool today" in *C. elegans*, *Drosophila*, plants, *Planaria* and trypanosome (*see* Hammond et al., Table 2). However, Hammond et al. characterize the use of RNAi in zebrafish, *Xenopus* and mouse embryo as "works, but some limitations" and the use of RNAi in mammalian cultured cells, mouse and human is characterized as "in the future" (*see* Hammond et al., Table 2). Furthermore, the expression of PADPRP antisense RNA provided efficient reduction of PADPRP expression (*see* Rosenthal et al. p. 441 and Fig. 2). Therefore, there would be no motivation to substitute siRNA for the successful use of antisense RNA in the experiments described by Rosenthal et al.

Further, at the time of filing the present application, one of ordinary skill in the art would not have even expected that oligonucleotides that are 12 to 24 nucleotides in length – as recited in the present claims – would traverse a gap junction (let alone the oligonucleotide of about 3,900 nucleotides in Rosenthal et al.). To the contrary, as discussed in the attached Declaration, it was believed by those skilled in the art that gap junctions would generally not allow molecules larger than about 1 kDa to pass and that molecules 1.9 kDa or larger would not permeate a gap junction channel (see the Declaration of Dr. Cohen at ¶¶ 15-18). The molecular weight of a single-stranded, 12 nucleotide long oligonucleotide ranges from about 3.4 kDa to about 4.1 kDa depending upon the nucleotide composition and longer oligonucleotides have even higher molecular weights. Thus, oligonucleotides such as siRNAs were significantly larger than what was believed by those of ordinary skill in the art to traverse gap junctions at the time of filing. Therefore, even with improper hindsight, Rosenthal et al. would not have been motivated to substitute siRNA for the antisense RNA.

Moreover, even with the impermissible use of hindsight, there would be no motivation for Rosenthal et al. to substitute siRNA for the antisense RNA because Rosenthal et al. were studying the effect of reducing the expression of a gene, PADPRP, only in the cells expressing the antisense oligonucleotide and not in any "target" cells (*i.e.*, not in the dermis of the nude mouse). It would have been contrary to Rosenthal et al. to provide modifications that would result in transferring a PADPRP inhibitory oligonucleotide from the implanted cells to the nude mouse dermis. Therefore, the assertion that Rosenthal et al. would have been motivated to substitute siRNA for the PADPRP antisense RNA is contrary to the teachings of Rosenthal et al. In addition, even with impermissible hindsight knowledge, it would have been contrary to Rosenthal et al. to substitute siRNA or any other oligonucleotide that would traverse a gap junction into cells of the nude mouse. As mentioned, Rosenthal et al. sought to study the effect of reducing PADPRP expression in the implanted cells, not the effect in the cells of the nude mouse.

II. Second Rejection Under 35 U.S.C. § 103(a)

The Examiner also alleges that claims 1-5, 7-9, 11, 12, and 20-23 are not patentable under 35 U.S.C. 103(a) over Giampuzzi et al. (Journal of Biological Chemistry, 2001 Vol. 276, pp. 29226-29232), as evidenced by Valiunas et al. (Journal of Physiology,

2005 Vol. 568, pp. 459-468), in view of Hammond et al. (Nature Reviews. Genetics, 2001 Vol. 2, pp.110-119).

The Office acknowledges that "Giampuzzi et al. do not explicitly state that the oligonucleotide is delivered to the target cell from the donor cell by traversing the gap junction" (Office Action dated Oct. 28, 2009 at p. 10). Rather the Office Action alleges that Giampuzzi et al. implicitly teach the claimed methods stating that the Office is "interpreting that the oligonucleotide is delivered to the target cell from the donor cell by traversing the gap junction, absent evidence to the contrary." (Office Action dated Oct. 28, 2009 at p. 10).

A. The Office Has Failed to Establish a Prima Facie Case

The Office states that "since the method steps recited in Applicant's claims are the same method steps as taught by Giampuzzi et al., the Examiner is interpreting that the oligonucleotide is delivered to the target cell from the donor cell by traversing the gap junction, absent evidence to the contrary." However, before the Office can shift the burden to the applicant, it must first present a prima facie case. For the reasons described below, Applicants submit that the Office has failed to present a prima facie case.

The assertion by the Office assuming that the LOX antisense RNA in Giampuzzi et al. traverses gap junctions absent evidence to the contrary are not sufficient to establish a prima facie case of obviousness. The Office must provide a rationale or evidence tending to show inherency. The fact that a certain result may occur in the prior art is not sufficient to establish the inherency of that result (*See* MPEP 2112; *See also Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990), which states "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." (emphasis in original).

In the present Office Action, no such basis has been provided and therefore no prima facie case has been established. In this regard, Applicants note that the claims were previously amended to recite oligonucleotides that are 12 to 14 nucleotides in length in contrast to the LOX antisense RNA used by Giampuzzi et al., which is about 1,018 nucleotides in length. As discussed below and explained in the attached Declaration by Dr. Ira Cohen, the antisense oligonucleotides in Giampuzzi et al. would not traverse a gap junction. Further, the evidence of record, as discussed below, indicates that one of skill in

the art would not even have expected that oligonucleotides 12 to 24 nucleotides in length (including siRNAs) would traverse gap junctions.

B. None of the References Teach or Suggest the Claimed Methods

None of the references cited teach or suggest a method of delivering an oligonucleotide into a target cell comprising: a) introducing the oligonucleotide or a plasmid expressing the oligonucleotide into a donor cell in vitro; and b) contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel composed of connexin 43 with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell by traversing the gap junction and wherein the oligonucleotide is 12-24 nucleotides in length. The cited art does not teach or suggest the claimed methods for at least the reasons described below.

1. Giampuzzi et al. Do Not Teach or Suggest the Claimed Methods

Giampuzzi et al. do not teach or suggest the claimed methods. The methods described by Giampuzzi et al. are designed to study the effect of reducing the expression of a target gene only in the cells expressing the antisense oligonucleotide. Giampuzzi et al. examine the role of lysyl oxidase (LOX) as a tumor suppressor by reducing the expression of LOX in rat kidney fibroblasts by the stable expression of LOX cDNA in the antisense orientation. These cells were injected subcutaneously into nude mice to study the tumorigenicity of the rat kidney fibroblasts expressing antisense LOX cDNA. The methods described by Giampuzzi et al. were not designed or intended to study the effects of LOX antisense in the host nude mouse cells. Therefore, the Office's assertion that Giampuzzi et al. implicitly practice the claimed methods is contrary to the teachings of Giampuzzi et al. For this reason, Giampuzzi et al. do not teach or suggest the methods of the present invention.

2. The Antisense RNA Used by Giampuzzi et al. Will Not Traverse Gap Junctions

The Office takes the position that Giampuzzi et al. implicitly teach the claimed method stating that the Office is "interpreting that the oligonucleotide is delivered to the target cell from the donor cell by traversing the gap junction, absent evidence to the contrary." (Office Action dated Oct. 28, 2009 at p. 10).

However, the antisense RNA used by Giampuzzi is too large to traverse a gap junction. The antisense RNA disclosed by Giampuzzi et al. contains the fragment from -33 to +985 of the mouse LOX cDNA in antisense orientation. Thus, this LOX antisense RNA is about 1,018 nucleotides in length. As explained in the Rule 1.132 Declaration by Dr. Ira Cohen, attached hereto, an antisense RNA of that length will not traverse a gap junction. Thus, even if the rat kidney fibroblasts expressing LOX antisense RNA were able to form gap junctions with cells in the nude mouse, the antisense RNA could not traverse the gap junctions (see the Declaration of Dr. Cohen at ¶¶ 10, 13-14). For this reason also, Giampuzzi et al. do not teach or suggest the methods of the present invention.

Moreover, in a previous rejection based on 35 U.S.C. § 112 ¶ 1, which was withdrawn in the present Office Action, the Office characterizes Valiunas et al. as teaching limitations on the length of oligonucleotides that can traverse a gap junction.[2] For example, the previous Office Action states:

> The Examiner has found in the prior art that **only oligonucleotides of 12-24 nucleotides in lengths are able to traverse gap junctions composed of Cx43**. See Valiunas et al. (J. Physiol 568.2:459-468, 2005).

Office Action dated July 6, 2009 at 8 (emphasis added).

> Thus, although the specification contemplates the use of any oligonucleotide, including plasmid DNA expressing oligonucleotides, such a disclosure would not be considered enabling since **Valiunas et al. teach that the length of the oligonucleotide plays an important factor in gap junction traversal.**

Office Action dated July 6, 2009 at 9 (emphasis added).

> As the reference of Valiunas et al. above indicates, **the rate of gap junction channel traversal is dependent on the length of the oligonucleotide**.

Office Action dated July 6, 2009 at 10 (emphasis added). Thus, according to the previous Office Action Valiunas et al. provide evidence that only oligonucleotides 12 to 24 nucleotides in length can traverse a gap junction. However, in the current Office Action

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[2] While not conceding the Examiner's characterization of Valiunas et al., the present claims were amended without prejudice to recite oligonucleotides of 12 to 24 nucleotides in length. As indicated below, the data presented by Dr. Cohen in the attached Rule 1.132 Declaration, demonstrates that the LOX antisense oligonucleotide of Giampuzzi et al. would not traverse a gap junction.

the Office is asserting that absent evidence to the contrary, an antisense oligonucleotide that is about 1,018 nucleotides in length is able to traverse a gap junction. For the reasons provided, the Office has not established a prima facie case and in any event, the antisense RNA disclosed by Giampuzzi et al. will not traverse a gap junction.

C. One of Skill in the Art Would Not Have Been Motivated to Substitute an siRNA for the Antisense RNA Used by Giampuzzi et al.

The Office Action states that "one of ordinary skill in the art would have been motivated to substitute the antisense oligonucleotide taught by Giampuzzi et al. with an oligonucleotide that is 12-24 nucleotides in length, such as a siRNA, since Hammond et al. taught that RNA interference is superior to antisense." (Office Action dated Oct. 28, 2009 at 11).

However, one of skill in the art would not have been motivated by the teachings of Hammond et al. to substitute a siRNA for the antisense RNA used by Giampuzzi et al. to reduce expression of LOX in rat kidney fibroblasts. In fact, according to Hammond et al., RNAi was "a tool today" in *C. elegans*, *Drosophila*, plants, *Planaria* and trypanosome (see Table 2). However, Hammond et al. characterized the use of RNAi in zebrafish, *Xenopus* and mouse embryo as "works, but some limitations" and the use of RNAi in mammalian cultured cells, mouse and human as "in the future" (see Table 2). Furthermore, the expression of LOX antisense RNA provided efficient reduction of LOX expression (*see* Giampuzzi et al. p. 29227 and Fig. 2). Therefore, there would be no motivation to substitute siRNA for the successful use of antisense RNA in the experiments described by Giampuzzi et al.

Further, at the time of filing the present application, one of skill in the art would not have even expected that oligonucleotides that are 12 to 24 nucleotides in length – as recited by the present claims – would traverse a gap junction (let alone the oligonucleotide of about 1,018 nucleotides in Giampuzzi et al.). To the contrary, as discussed in the attached Declaration, it was believed by those skilled in the art that gap junctions would generally not allow molecules larger than about 1 kDa to pass and that molecules 1.9 kDa or larger would not permeate a gap junction channel (see the Declaration of Dr. Cohen at ¶¶ 15-18). The molecular weight of a single-stranded, 12 nucleotide long oligonucleotide ranges from about 3.4 kDa to about 4.1 kDa depending upon the nucleotide composition. Thus, oligonucleotides such as siRNAs were significantly larger that what was believed by

those of ordinary skill in the art to traverse gap junctions at the time of filing. Therefore, even with improper hindsight, Giampuzzi et al. would not have been motivated to substitute siRNA for the antisense RNA.

Moreover, even with the impermissible use of hindsight, there would be no motivation for Giampuzzi et al. to substitute siRNA for the antisense RNA because they were studying the effect of reducing the expression of the LOX gene, only in the rat kidney fibroblasts expressing the antisense oligonucleotide and not in any "target" cells (*i.e.*, not in the cells of the nude mouse). It would have been contrary to Giampuzzi et al. to provide modifications that would result in transferring a LOX inhibitory oligonucleotide from the implanted cells to the cells of the nude mouse. Thus, the assertion that Giampuzzi et al. would have been motivated to substitute siRNA for the LOX antisense RNA is contrary to the teachings of Giampuzzi et al. In addition, even with impermissible hindsight knowledge, it would have been contrary to Giampuzzi et al. to substitute siRNA or any other oligonucleotide that would traverse a gap junction into cells of the nude mouse. As mentioned, Giampuzzi et al. seek to study the effect of reducing LOX expression in the implanted cells, not the effect in the cells of the nude mouse.

III. None of the Art Cited Teach or Suggest the Claimed Method Wherein the Donor Cell is a Human Mesenchymal Stem Cell

Original claim 9 recites "[t]he method of claim 1, wherein the donor cell is a human mesenchymal stem cell." In addition, new claims 25 to 28 also recite "wherein the donor cell is a human mesenchymal stem cell" and depend from independent claims 20 to 22, respectively.

As discussed above, the art cited by the Office does not teach or suggest a method of delivering an oligonucleotide into a target cell comprising: a) introducing the oligonucleotide or a plasmid expressing the oligonucleotide into a donor cell in vitro; and b) contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel comprising connexin 43 with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell by traversing the gap junction and wherein the oligonucleotide is 12-24 nucleotides in length.

Moreover, the art cited by the Office does not teach or suggest the claimed methods wherein the donor cell is a human mesenchymal stem cell. Rather, Rosenthal et al. specifically study the effects of selectively lowering the levels of PADPRP enzyme in

cultured human keratinocytes by stably expressing the PADPRP antisense RNA in the cultured human keratinocytes and in reconstituted skin grafts made from these keratinocytes. Giampuzzi et al. examine the role of lysyl oxidase (LOX) as a tumor suppressor by reducing the expression of LOX in rat kidney fibroblasts by the stable expression of LOX cDNA in the antisense orientation. These cells were injected subcutaneously in nude mice to study the tumorigenicity of the rat kidney fibroblasts expressing antisense LOX cDNA. Thus, neither Rosenthal et al. nor Giampuzzi et al. (nor any of the other prior art cited in this Office Action) teach or suggest the claimed methods wherein the donor cell is a human mesenchymal stem cell. For this reason, at least, these dependant claims are not obvious in view of the art cited by the Office.

IV. Conclusion

The present Office Action is the third time that new grounds for rejection of the claims have been raised by the Office. All previous rejections have been withdrawn. However, the Office again raised new grounds for rejection of the claims, this time under § 103(a).

Applicants submit that the present response addresses the Examiner's obviousness rejections and that the present application is in condition for allowance. Thus, Applicants respectfully request that the Office pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

The Office is authorized to charge any additional fees that may be necessary for consideration of this paper, or to credit any overpayment, to Kenyon & Kenyon Deposit Account No. 11-0600.

Respectfully submitted,

Dated: April 28, 2010

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